OTHR-12. THE DEVELOPMENT OF MACHINE LEARNING ALGORITHMS FOR THE DIFFERENTIATION OF GLIOMA AND BRAIN METASTASES – A SYSTEMATIC REVIEW

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PURPOSE: Medical staging, surgical planning, and therapeutic decisions are significantly different for brain metastases versus gliomas. Machine learning (ML) algorithms have been developed to differentiate these pathologies. We performed a systematic review to characterize ML methods and to evaluate their accuracy. METHODS: Studies on the application of machine learning in neuro-oncology were searched in Ovid Embase, Ovid MEDLINE, Cochrane trials (CENTRAL) and Web of science core-collection. A search strategy was designed in compliance with a clinical librarian and confirmed by a second librarian. The search strategy comprised of controlled vocabulary including artificial intelligence, machine learning, deep learning, magnetic resonance imaging, and glioma. The initial search was performed in October 2020 and then updated in February 2021. Candidate articles were screened in Covidence by at least two reviewers each. A bias analysis was conducted in agreement with TRIPOD, a bias assessment tool similar to CLAIM. RESULTS: Twenty-nine articles were used for data extraction. Four articles specified model development for solitary brain metastases. Classical ML (cML) algorithms represented 85% of models used, while deep learning (DL) accounted for 15%. cML algorithms performed with an average accuracy, sensitivity, and specificity of 82%, 78%, 88%, respectively; DL performed 84%, 79%, 81%. The support vector machine (SVM) algorithm was the most common used cML model in the literature and convolutional neural networks (CNN) were standard for DL models. We also found T1, T1 post-gadolinium and T2 sequences were most commonly used for feature extraction. Preliminary TRIPOD analysis yielded an average score of 14.25 (range 8–18). CONCLUSION: ML algorithms that can accurately classify glioma from brain metastases have been developed. SVM and CNN are leading approaches with high accuracy. Standardized algorithm performance reporting is a clear limitation to be addressed in future studies.

OTHR-13. IMPACT THE BRAIN: IMPROVING METASTATIC BREAST CANCER PATIENT ACCESS TO COORDINATED TREATMENT.

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Central nervous system (CNS) metastases are associated with decreased survival and quality of life for patients with metastatic breast cancer (MBC). Multi-disciplinary care can optimize outcomes. This project aims to improve access to coordinated care for patients with MBC and CNS metastases. Patients with MBC and CNS metastases are referred and offered to enroll in our care coordination program. A team consisting of specialists (breast medical oncology, breast cancer genetics, radiation oncology, neurosurgery, neuro-oncology, physical medicine and rehabilitation (PM&R), neuropsychology, and palliative care) supports a dedicated program coordinator who provides navigation, education, specialty referral, and clinical trial screening. A unique intake form developed for the program creates personalized, coordinated, and expedited referrals. Patient-reported outcomes and caregiver burden assessments are collected. Since May 2020, 43 patients were referred and a total of 40 patients (93%) were enrolled – 2 (5%) declined due to perceived burden of participation and 1 (2%) died before enrollment. 85% of patients were Caucasian (n = 34) and 15% were non-Caucasian (n=6). Median time to program intake was 1 day (range: 0–8 days). Of the 43 patients referred, 17 (40%) consented to research studies in the metastatic setting. 11 were for an interventional trial (65%), while 9 consents were for non-interventional studies (53%). In addition to the initially referred specialty, 56 referrals were made across 7 sub-specialties; 37 patients (66%) were subsequently seen by a sub-specialist, most commonly radiation oncology (n = 9), neuro-oncology (n=8), PM&R (n=8), and neuropsychology (n=8). Implementation of a care coordination program for patients with MBC and CNS metastases is feasible. Further, it allows for improved access to care across sub-specialties and supports participation in clinical research for a group of cancer patients historically underrepresented in research studies.

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OTHR-14. AN IMMUNOGENOMIC ANALYSIS OF MELANOMA BRAIN METASTASES (MBM) COMPARED TO EXTRACRANIAL METASTASES (ECM)

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BACKGROUND: MBM have a unique molecular profile compared to ECM. METHODS: We analyzed a previously published dataset from MD Anderson Cancer Center, including RNA-seq on surgically resected, FFPE MBM and ECM from the same patients. STAR pipeline was used to estimate mRNA abundance. DESeq2 package was used to perform differential gene expression (DGE) analyses. Pathway analysis was performed using Gene Set Enrichment Analysis (GSEA). Paired DGE and GSEA compared MBM vs. lymph node (LN) metastases (n = 16) and MBM vs. skin mets (n = 10). CIBERSORTx estimated relative abundance of immune cell types in MBM and ECM. GATK Mutect2 pipeline was used to call somatic mutations using paired normal tumor samples. Mutations were annotated using the Ensembl Variant Effect Predictor and visualized using the Maftools package in R. RNA-seq was available on 54 human primary cutaneous melanomas (CM). Gene Ontology or KEGG Pathway analysis was performed using goana function of limma package in R. RESULTS: Paired GSEA found that autophagy pathways may be up-regulated in MBM vs. LN and MBM vs. skin mets. On a single-gene level, the most strongly up-regulated genes in autophagy pathways were *GFAP* and *HBB*. Fold changes in other autophagy-related genes were low and did not reach significance. Comparison between CM which recurred in brain vs. CM which did not recur identified up-regulation of autophagy pathways. CIBERSORTx identified an increased proportion of immune suppressive M2 macrophages compared to tumor suppressive M1 macrophages in MBMs and ECMs. CONCLUSION: Up-regulation of autophagy pathways was observed in patient-matched MBM vs. LN and skin mets. This finding was driven by up-regulation of *GFAP* and *HBB*, which could reflect changes in the tumor microenvironment. Higher M2:M1 ratio may contribute to an immune suppressive tumor microenvironment and may be targetable. Validation of our findings in an independent Duke dataset is ongoing.

OTHR-15. ASSESSMENT OF TRIPOD ADHERENCE IN ARTICLES DEVELOPING MACHINE LEARNING MODELS FOR DIFFERENTIATION OF GLIOMA FROM BRAIN METASTASIS

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PURPOSE: Machine learning (ML) applications in predictive models in neuro-oncology have become an increasingly investigated subject of research. For their incorporation into clinical practice, rigorous assessment is needed to reduce bias. Several reports have indicated utility of ML applications in differentiation of glioma from brain metastasis. However, a systematic assessment of quality of methodology and reporting in these studies has not been done yet. We examined the adherence of 29 published reports in this field to the TRIPOD statement, which is similar to CLAIM checklist. MATERIALS AND METHODS: Our systematic review was conducted in accordance with PRISMA guidelines. Ovid Embase, Ovid MEDLINE, Cochrane trials (CENTRAL) and Web of science core-collection were searched. Keywords included artificial intelligence, machine learning, deep learning, radiomics, magnetic resonance imaging, glioma, and glioblastoma. Assessment of TRIPOD adherence in 29 eligible studies was performed. Individual item performance was assessed by adherence index (ADI), the ratio of mean achieved score to maximum score per TRIPOD item. RESULTS: In a preliminary analysis of 8 studies, the average TRIPOD adherence score was 0.48 (14.25/30 items fulfilled) with individual scores ranging from 0.27 (8/30) to 0.60 (18/30). Best overall item performance, with an ADI of 1, was seen in item 3 (Background/Objectives), 16 (Model performance) and 19 (Interpretation). Poorest performance was detected in item 1 (Title) and 2 (Abstract), followed by item 9 (Missing Data) with ADI of 0, 0 and 0.13, respectively. CONCLUSION: Preliminary results underline the lack of reproducibility in ML studies on distinction between glioma and brain metastasis. An average TRIPOD adherence score of 0.48 indicates insufficient quality of reporting and outlines the need for increased utilization of quality scoring

systems in study documentation. Systematic evaluation of quality score adherence will allow us to identify common flaws in this field for enabling translation of models into clinical workflow.

RADIATION

RADI-01. CYSTIC BRAIN METASTASES MANAGED WITH RESERVOIR PLACEMENT AND STEREOTACTIC RADIOSURGERY

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BACKGROUND: Stereotactic radiosurgery (SRS) has become a mainstay of treatment for patients with metastatic brain tumors. However, metastatic tumors with a large cystic component often exceed the size limit for safe and effective SRS. In such cases, surgical resection may not be the preferred first method of treatment, due to tumor location, patient co-morbidities, and patient preference. In such cases volume reduction by cyst aspiration followed by SRS may be a preferred option. METHODS: Seven patients were treated with this method. We performed reservoir insertion for the aspiration of cystic component in each patient and followed that with outpatient SRS. RESULTS: Mean overall volume reduction from this treatment method was 80% (range 46.5–94.9). Mean volume reduction from the cyst aspiration alone was 60.7% (range 3.5–90.9), and after SRS a further 71.6% (range 34.6–94.4), accounting for some cyst reaccumulation between the time of surgery and SRS. The interval between those two procedures were 24 days on average (range 11–58 days). Repeat reservoir aspiration was done a total of 10 times in 5 patients. CONCLUSION: Cyst aspiration with reservoir placement followed by SRS is a good option for patients with large cystic brain metastases. The reservoir allows for repeat aspiration if needed. Catheter placement at the center of the cyst, and SRS within 2–3 weeks of surgery, can maximize the likelihood of a successful outcome.

RADI-02. HIPPOCAMPAL-SPARING WHOLE BRAIN VOLUMETRIC MODULATED ARC THERAPY (VMAT) PLANNING IN MONACO: A "HOW-TO" NOT PULL YOUR HAIR OUT.

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PURPOSE: NRG-CC001 recently reported positive results on hippocampal-sparing IMRT (HS-IMRT) in conjunction with memantine for the reduction in cognitive decline compared to conventional whole brain radiation therapy. Herein, we report our experience in planning volumetric modulated arc therapy (VMAT) cases in Monaco® with the anticipation of increased utilization of the planning technique for delivery on Elekta linear accelerators. METHODS AND MATERIALS: Twelve patients previously treated with whole brain radiation therapy who would have been eligible for NRG-CC001 were replanned with VMAT HS-IMRT for to a dose of 30Gy/10fx using constraints from the trial. RESULTS: All twelve patients were able to be planned with VMAT and achieve NRG-CC001 dose constraints. Median maximum and D100% to the right and left hippocampi were: 13.37Gy and 13.43Gy, respectively and 8.76Gy and 8.86Gy, respectively. Median coverage of the brain minus the hippocampi with 30Gy was 96.53%. All cases passed quality assurance testing with 3%/3mm and 2%/2mm criterion. CONCLUSIONS: Hippocampal-sparing IMRT whole brain radiation therapy can be feasibly planned with VMAT technique in Monaco® and delivered on Elekta linear accelerators.

RADI-03. A STRATEGY TO PERSONALIZE THE USE OF RADIATION IN PATIENTS WITH BRAIN METASTASIS BASED ON S100A9-MEDIATED RESISTANCE

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Finding effective treatment options for patients with brain metastasis remains an unmet need. Given the limitations imposed by the blood-brain-barrier for systemic approaches, radiotherapy offers a superior ability to access the brain. While clinical practice recently adapted the use of stereotactic radiosurgery (SRS), Whole-Brain-Radiotherapy (WBRT) continuous to be an important treatment option, since many patients present with multifocal lesions or bad performance scores, rendering them ineligible for SRS. Unfortunately, overall survival of patients remains unaffected by radiotherapy. Despite this clinical data, the molecular mechanisms that allow metastatic cells to resist radiotherapy in the brain is unknown. We have applied WBRT to experimental brain metastasis from lung and breast adenocarcinoma and validated their resistance *in vivo*. An unbiased search to identify potential mediators of resistance identified the S100A9-RAGE-NFkB-JunB pathway. Targeting this pathway genetically reverts the resistance to radiotherapy and increases therapeutic benefits *in vivo*. In two independent cohorts of brain metastasis from lung and breast adenocarcinoma patients, levels of S100A9 correlate with the response to radiotherapy, offering a novel approach to stratify patients according to their expected benefit. In order to make this biomarker also available for brain metastasis patients receiving palliative WBRT without preceding surgery, we complemented our tumor-specimen based approach with the less invasive detection of S100A9 from liquid biopsies. Here, serum S100A9 also correlated with a worse response to WBRT in brain metastasis patients. Furthermore, we have validated the use of a blood-brain-barrier permeable RAGE inhibitor to restore radio-sensitivity in experimental brain metastasis models *in vivo* and in patient-derived organotypic cultures of radio-resistant brain metastasis *ex vivo*. In conclusion, we identified S100A9 as a major mediator of radio-resistance in brain metastasis and offer the molecular framework to personalize radiotherapy by exploiting it as a biomarker and as a therapeutic target, thus maximizing the benefits for the patient.

RADI-04. STEREOTACTIC RADIOSURGERY IN ALVEOLAR SOFT PART SARCOMA BRAIN METASTASIS

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BACKGROUND: Alveolar soft part sarcoma (ASPS), although rare, has the highest incidence of brain metastasis amongst all sarcomas. Stereotactic radiosurgery (SRS) has been shown to be a well tolerated and effective treatment of intracranial sarcomatous metastasis. However, there is a paucity of published literature that guides radiation therapy in this condition. METHODS: This is a single centre retrospective review of all ASPS patients with intraparenchymal brain metastasis in our centre treated with stereotactic radiosurgery (SRS). SRS dosing is dichotomised into high and low dose (≥25 Gy and <25 Gy respectively) and outcomes such as local recurrence (LR) and radiation effects are noted. Successful treatment was defined as a lesion that regressed, is stable, or has less than 25% increase in tumour volume. Local recurrence (LR) was defined as increase in tumour volume by more than 25% during follow up. RESULTS: There were three patients with 11 ASPS metastatic brain lesions, one of which underwent retreatment. Each lesion was followed up for a mean duration of 12 months (range: 5 – 22 months). Five lesions treated with a high dose regime and six lesions were given low dose. Lesions treated with high dose SRS experienced significantly less LR (20% vs 83.3%, OR 20.0 [95%CI 0.93 – 430), p = 0.036) with no increase in undue symptomatic radiation effects. Retreatment of lesions with LR after initial SRS using a low dose regime was successful, albeit only in the single recurrent lesion. CONCLUSIONS: We conclude that SRS can be used as a first line treatment for ASPS brain metastasis that are not surgically accessible and that using a high dose for treatment is effective and safe. Multicentre collaborative studies can be performed to validate this claim.

RADI-05. METASTATIC NEOPLASM VOLUME KINETICS FOLLOWING TWO-STAGED STEREOTACTIC RADIOSURGERY

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INTRODUCTION: Multisession staged stereotactic radiosurgery (2-SSRS) represents an alternative approach for management of large brain metastases (LBMs), with potential theoretical advantages over fractionated SRS and rep-